Primary familial brain calcification

Primary familial brain calcification is a condition characterized by abnormal deposits of calcium (calcification) in blood vessels within the brain. These calcium deposits are visible only on medical imaging and typically occur in the basal ganglia, which are structures deep within the brain that help start and control movement of the body. Other brain regions may also be affected.

The main signs and symptoms of primary familial brain calcification are movement disorders and psychiatric or behavioral problems. These difficulties usually begin in mid-adulthood, and worsen over time. Most affected individuals have a group of movement abnormalities called parkinsonism, which include unusually slow movement (bradykinesia), muscle rigidity, and tremors. Other movement problems common in people with primary familial brain calcification include involuntary tensing of various muscles (dystonia), uncontrollable movements of the limbs (choreoathetosis), and an unsteady walking style (gait).

Psychiatric and behavioral problems occur in 20 to 30 percent of people with primary familial brain calcification. These problems can include difficulty concentrating, memory loss, changes in personality, a distorted view of reality (psychosis), and decline in intellectual function (dementia). Affected individuals may also have difficulty swallowing (dysphagia), impaired speech, headache, episodes of extreme dizziness (vertigo), seizures, or urinary problems.

The severity of primary familial brain calcification varies among affected individuals; some people have no symptoms related to the condition, whereas others have significant movement and psychiatric problems.

Frequency

Primary familial brain calcification was thought to be a rare disorder; however, because brain imaging tests are needed to see the calcium deposits, this condition is believed to be underdiagnosed. Recent research has indicated that primary familial brain calcification may occur in 2 to 6 per 1,000 people, with many affected individuals not showing signs and symptoms of the condition.

Causes

Primary familial brain calcification is caused by mutations in one of several genes. The most commonly mutated gene is called *SLC20A2*, and accounts for an estimated 40 percent of cases, followed by the *PDGFRB* gene, which is mutated in about 10 percent of cases. Changes in other genes each account for a small percentage of cases. In about half of individuals with primary familial brain calcification the genetic cause is

unknown. These individuals are thought to have mutations in genes that have not yet been linked to the condition.

The *SLC20A2* gene provides instructions for making a protein called sodium-dependent phosphate transporter 2 (PiT-2). This protein is highly active in nerve cells (neurons) in the brain where it plays a major role in regulating phosphate levels (phosphate homeostasis) by transporting phosphate across cell membranes. *SLC20A2* gene mutations lead to the production of a PiT-2 protein that cannot effectively transport phosphate into cells. As a result, phosphate levels in the bloodstream rise. In the brain, the excess phosphate combines with calcium and forms deposits within blood vessels in the brain.

The *PDGFRB* gene provides instructions for making a protein that transmits signals from the cell surface into the cell. These signals control a variety of cell processes. *PDGFRB* gene mutations result in a protein with impaired signaling ability. However, it is unclear how the mutations cause primary familial brain calcification. The altered signaling may result in an abnormally large amount of calcium entering the cells that line blood vessels in the brain, leading to calcification of these blood vessels. Alternatively, changes in PDGFRB signaling could disrupt processes that regulate levels of phosphate and calcium in brain cells, leading to the formation of calcium deposits. Other genes known to be associated with primary familial brain calcification also have roles in cell signaling and phosphate homeostasis.

Researchers suggest that calcium deposits lead to the features of primary familial brain calcification by disrupting the connections between the basal ganglia and other areas of the brain, particularly the frontal lobes. These areas at the front of the brain are involved in reasoning, planning, judgment, and problem-solving. The regions of the brain that regulate social behavior, mood, and motivation may also be affected.

Research has shown that people with significant calcification tend to have more signs and symptoms of primary familial brain calcification than people with little or no calcification. However, this association does not apply to all people with primary familial brain calcification.

Inheritance Pattern

In most cases, primary familial brain calcification is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person has one parent with the condition.

Less commonly, primary familial brain calcification is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- bilateral striopallidodentate calcinosis
- cerebrovascular ferrocalcinosis
- familial idiopathic basal ganglia calcification
- FIBGC
- striopallidodentate calcinosis

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Basal ganglia calcification, idiopathic, 4
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C3554321/
- Genetic Testing Registry: Basal ganglia calcification, idiopathic, 6
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C4225335/
- Genetic Testing Registry: BASAL GANGLIA CALCIFICATION, IDIOPATHIC, 7, AUTOSOMAL RECESSIVE
  https://www.ncbi.nlm.nih.gov/gtr/conditions/CN258198/
- Genetic Testing Registry: Idiopathic basal ganglia calcification 1
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C4551624/
- Genetic Testing Registry: Idiopathic basal ganglia calcification 5
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C3809645/

Other Diagnosis and Management Resources

- Dystonia Medical Research Foundation: Treatment
  https://dystonia-foundation.org/living-dystonia/treatment/
- GeneReview: Primary Familial Brain Calcification
  https://www.ncbi.nlm.nih.gov/books/NBK1421

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Basal Ganglia Dysfunction
  https://medlineplus.gov/ency/article/001069.htm
- Encyclopedia: Calcification
  https://medlineplus.gov/ency/article/002321.htm

- Health Topic: Brain Diseases
  https://medlineplus.gov/braindiseases.html
- Health Topic: Seizures
  https://medlineplus.gov/seizures.html

Genetic and Rare Diseases Information Center

- Primary Familial Brain Calcification
  https://rarediseases.info.nih.gov/diseases/6406/primary-familial-brain-calcification

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Fahr's Syndrome Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Fahrs-Syndrome-Information-Page

Educational Resources

- Kennedy Krieger Institute: Epilepsy (Seizure Disorder)
  https://www.kennedykrieger.org/patient-care/conditions/epilepsy-seizure-disorder
- Kennedy Krieger Institute: Movement Disorders
  https://www.kennedykrieger.org/patient-care/conditions/movement-disorders
- MalaCards: familial idiopathic basal ganglia calcification
  https://www.malacards.org/card/familial_idiopathic_basal_ganglia_calcification
- MalaCards: primary familial brain calcification
  https://www.malacards.org/card/primary_familial_brain_calcification
- Merck Manual Consumer Version: Dystonia
  https://www.merckmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/movement-disorders/dystonia
- Orphanet: Bilateral striopallidodentate calcinosis
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=1980

Patient Support and Advocacy Resources

- Dystonia Medical Research Foundation
  https://dystonia-foundation.org/
- Family Caregiver Alliance
  https://www.caregiver.org/
- National Ataxia Foundation
  https://ataxia.org/
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/primary-familial-brain-calcification/

Clinical Information from GeneReviews

- Primary Familial Brain Calcification
  https://www.ncbi.nlm.nih.gov/books/NBK1421

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28familial+idiopathic+basal+ganglia+calcification%5BTIAB%5D%29+OR+%28idiopathic+basal+ganglia+calcification%5BTIAB%5D%29+OR+%28fahr+disease%5BTIAB%5D%29+OR+%28fibgc%5BTIAB%5D%29+OR+%28fahr's+syndrome%5BTIAB%5D%29+OR+%28Primary+familial+brain+calcification%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- BASAL GANGLIA CALCIFICATION, IDIOPATHIC, 1
  http://omim.org/entry/213600
- BASAL GANGLIA CALCIFICATION, IDIOPATHIC, 4
  http://omim.org/entry/615007
- BASAL GANGLIA CALCIFICATION, IDIOPATHIC, 5
  http://omim.org/entry/615483
- BASAL GANGLIA CALCIFICATION, IDIOPATHIC, 6
  http://omim.org/entry/616413
- BASAL GANGLIA CALCIFICATION, IDIOPATHIC, 7, AUTOSOMAL RECESSIVE
  http://omim.org/entry/618317

Medical Genetics Database from MedGen

- Basal ganglia calcification, idiopathic 2
  https://www.ncbi.nlm.nih.gov/medgen/335757
- Basal ganglia calcification, idiopathic, 4
  https://www.ncbi.nlm.nih.gov/medgen/767235
- Basal ganglia calcification, idiopathic, 6
  https://www.ncbi.nlm.nih.gov/medgen/901404
- BASAL GANGLIA CALCIFICATION, IDIOPATHIC, 7, AUTOSOMAL RECESSIVE
  https://www.ncbi.nlm.nih.gov/medgen/941234
- Idiopathic basal ganglia calcification 1
  https://www.ncbi.nlm.nih.gov/medgen/1637664
- Idiopathic basal ganglia calcification 5
  https://www.ncbi.nlm.nih.gov/medgen/815975

Sources for This Summary

- Anheim M, López-Sánchez U, Giovannini D, Richard AC, Touhami J, N'Guyen L, Rudolf G, Thibault-Stoll A, Frebourg T, Hannequin D, Campion D, Battini JL, Sitbon M, Nicolas G. XPR1 mutations are a rare cause of primary familial brain calcification. J Neurol. 2016 Aug;263(8): 1559-64. doi: 10.1007/s00415-016-8166-4. Epub 2016 May 26.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27230854
- Arkadir D, Lossos A, Rahat D, Abu Snineh M, Schueler-Furman O, Nitschke S, Minassian BA, Sadaka Y, Lerer I, Tabach Y, Meiner V. MYORG is associated with recessive primary familial brain calcification. Ann Clin Transl Neurol. 2018 Nov 15;6(1):106-113. doi: 10.1002/acn3.684. eCollection 2019 Jan.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30656188
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6331209/
- Arts FA, Velghe AI, Stevens M, Renauld JC, Essaghir A, Demoulin JB. Idiopathic basal ganglia calcification-associated PDGFRB mutations impair the receptor signalling. J Cell Mol Med. 2015 Jan;19(1):239-48. doi: 10.1111/jcmm.12443. Epub 2014 Oct 8.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25292412
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4288366/
- Cen Z, Chen Y, Chen S, Wang H, Yang D, Zhang H, Wu H, Wang L, Tang S, Ye J, Shen J, Wang H, Fu F, Chen X, Xie F, Liu P, Xu X, Cao J, Cai P, Pan Q, Li J, Yang W, Shan PF, Li Y, Liu JY, Zhang B, Luo W. Biallelic loss-of-function mutations in JAM2 cause primary familial brain calcification. Brain. 2019 Dec 18. pii: awz392. doi: 10.1093/brain/awz392. [Epub ahead of print]
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31851307
- Chen S, Cen Z, Fu F, Chen Y, Chen X, Yang D, Wang H, Wu H, Zheng X, Xie F, Ouyang Z, Tang W, Zhang S, Yin L, Zhang Y, Meng P, Zhu X, Zhang H, Jiang F, Zhang K, He J, Zhang D, Ming H, Song D, Zhou Z, Luo Y, Gu Q, Su Y, Wu X, Tang H, Wu C, Chen W, Liu JY, Luo W; Chinese PFBC Study Group. Underestimated disease prevalence and severe phenotypes in patients with biallelic variants: A cohort study of primary familial brain calcification from China. Parkinsonism Relat Disord. 2019 Jul;64:211-219. doi: 10.1016/j.parkreldis.2019.04.009. Epub 2019 Apr 11.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31003906
- Chen Y, Fu F, Chen S, Cen Z, Tang H, Huang J, Xie F, Zheng X, Yang D, Wang H, Huang X, Zhang Y, Zhou Y, Liu JY, Luo W. Evaluation of MYORG mutations as a novel cause of primary familial brain calcification. Mov Disord. 2019 Feb;34(2):291-297. doi: 10.1002/mds.27582. Epub 2018 Dec 27.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30589467
- Grütz K, Volpato CB, Domingo A, Alvarez-Fischer D, Gebert U, Schifferle G, Buffone E, Wszolek ZK, Rademakers R, Ferbert A, Hicks AA, Klein C, Pramstaller PP, Westenberger A. Primary familial brain calcification in the 'IBGC2' kindred: All linkage roads lead to SLC20A2. Mov Disord. 2016 Dec; 31(12):1901-1904. doi: 10.1002/mds.26768. Epub 2016 Sep 27.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27671522

- Hsu SC, Sears RL, Lemos RR, Quintáns B, Huang A, Spiteri E, Nevarez L, Mamah C, Zatz M, Pierce KD, Fullerton JM, Adair JC, Berner JE, Bower M, Brodaty H, Carmona O, Dobricic V, Fogel BL, García-Estevez D, Goldman J, Goudreau JL, Hopfer S, Jankovic M, Jaumà S, Jen JC, Kirdlarp S, Klepper J, Kostic V, Lang AE, Linglart A, Maisenbacher MK, Manyam BV, Mazzoni P, Miedzybrodzka Z, Mitarnun W, Mitchell PB, Mueller J, Novakovic I, Paucar M, Paulson H, Simpson SA, Svenningsson P, Tuite P, Vitek J, Wetchaphanphesat S, Williams C, Yang M, Schofield PR, de Oliveira JR, Sobrido MJ, Geschwind DH, Coppola G. Mutations in SLC20A2 are a major cause of familial idiopathic basal ganglia calcification. Neurogenetics. 2013 Feb;14(1):11-22. doi: 10.1007/s10048-012-0349-2. Epub 2013 Jan 20.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23334463
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4023541/
- Nicolas G, Charbonnier C, Campion D, Veltman JA. Estimation of minimal disease prevalence from population genomic data: Application to primary familial brain calcification. Am J Med Genet B Neuropsychiatr Genet. 2018 Jan;177(1):68-74. doi: 10.1002/ajmg.b.32605. Epub 2017 Nov 20.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29152850
- Nicolas G, Charbonnier C, de Lemos RR, Richard AC, Guillin O, Wallon D, Legati A, Geschwind D, Coppola G, Frebourg T, Campion D, de Oliveira JR, Hannequin D; collaborators from the French IBGC study Group. Brain calcification process and phenotypes according to age and sex: Lessons from SLC20A2, PDGFB, and PDGFRB mutation carriers. Am J Med Genet B Neuropsychiatr Genet. 2015 Oct;168(7):586-94. doi: 10.1002/ajmg.b.32336. Epub 2015 Jun 30.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26129893
- Nicolas G, Pottier C, Maltête D, Coutant S, Rovelet-Lecrux A, Legallic S, Rousseau S, Vaschalde Y, Guyant-Maréchal L, Augustin J, Martinaud O, Defebvre L, Krystkowiak P, Pariente J, Clanet M, Labauge P, Ayrignac X, Lefaucheur R, Le Ber I, Frébourg T, Hannequin D, Campion D. Mutation of the PDGFRB gene as a cause of idiopathic basal ganglia calcification. Neurology. 2013 Jan 8;80(2):181-7. doi: 10.1212/WNL.0b013e31827ccf34. Epub 2012 Dec 19.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23255827
- Ramos EM, Carecchio M, Lemos R, Ferreira J, Legati A, Sears RL, Hsu SC, Panteghini C, Magistrelli L, Salsano E, Esposito S, Taroni F, Richard AC, Tranchant C, Anheim M, Ayrignac X, Goizet C, Vidailhet M, Maltete D, Wallon D, Frebourg T, Pimentel L, Geschwind DH, Vanakker O, Galasko D, Fogel BL, Innes AM, Ross A, Dobyns WB, Alcantara D, O'Driscoll M, Hannequin D, Campion D; French PFBC study group, Oliveira JR, Garavaglia B, Coppola G, Nicolas G. Primary brain calcification: an international study reporting novel variants and associated phenotypes. Eur J Hum Genet. 2018 Oct;26(10):1462-1477. doi: 10.1038/s41431-018-0185-4. Epub 2018 Jun 28.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29955172
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6138755/
- Wang C, Li Y, Shi L, Ren J, Patti M, Wang T, de Oliveira JR, Sobrido MJ, Quintáns B, Baquero M, Cui X, Zhang XY, Wang L, Xu H, Wang J, Yao J, Dai X, Liu J, Zhang L, Ma H, Gao Y, Ma X, Feng S, Liu M, Wang QK, Forster IC, Zhang X, Liu JY. Mutations in SLC20A2 link familial idiopathic basal ganglia calcification with phosphate homeostasis. Nat Genet. 2012 Feb 12;44(3):254-6. doi: 10.1038/ng.1077.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22327515
- Yao XP, Cheng X, Wang C, Zhao M, Guo XX, Su HZ, Lai LL, Zou XH, Chen XJ, Zhao Y, Dong EL, Lu YQ, Wu S, Li X, Fan G, Yu H, Xu J, Wang N, Xiong ZQ, Chen WJ. Biallelic Mutations in MYORG Cause Autosomal Recessive Primary Familial Brain Calcification. Neuron. 2018 Jun 27;98(6):1116-1123.e5. doi: 10.1016/j.neuron.2018.05.037. Epub 2018 Jun 14.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29910000

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/primary-familial-brain-calcification

Reviewed: January 2020
Published: June 23, 2020

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services